

0847, 623

(FILE 'HOME' ENTERED AT 14:51:36 ON 25 JUL 2003)

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:51:45 ON 25 JUL 2003

L1 326 S (DYRBERG, T? OR DYRBERG T?)/AU, IN
L2 50 S (WORSAAE, A? OR WORSAAE A?)/AU, IN
L3 15 S L1 AND L2
L4 7 DUP REM L3 (8 DUPLICATES REMOVED)
L5 361 S L1 OR L2
L6 346 S L5 NOT L3
L7 234 S L6 AND INSULIN?
L8 0 S L7 AND B25
L9 1 S L6 AND (INSULIN?) (3A) (ANALOG?)

FILE 'STNGUIDE' ENTERED AT 14:54:23 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:57:43 ON 25 JUL 2003

L10 8 S (MANDIC, J? OR MANDIC J?)/AU, IN
L11 8 DUP REM L10 (0 DUPLICATES REMOVED)
L12 32 S (B25) (5A) (ASP?)
L13 17 DUP REM L12 (15 DUPLICATES REMOVED)
L14 11 S L13 AND INSULIN?

FILE 'STNGUIDE' ENTERED AT 15:06:45 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:08:15 ON 25 JUL 2003

FILE 'STNGUIDE' ENTERED AT 15:09:32 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:10:15 ON 25 JUL 2003

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1990:491524 CAPLUS
DN 113:91524
TI Identification of residues in the **insulin** molecule important for binding to **insulin-degrading enzyme**
AU Affholter, Joseph A.; Cascieri, Margaret A.; Bayne, Marvin L.; Brange, Jens; Casaretto, Monika; Roth, Richard A.
CS Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SO Biochemistry (1990), 29(33), 7727-33
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English

=> d 5 ab,

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AB **Insulin-degrading enzyme (IDE)** hydrolyzes **insulin** at a limited no. of sites. Although the positions of these cleavages are known, the residues of **insulin** important in its binding to IDE have not been defined. To this end, the binding of a variety of **insulin** analogs to the protease was studied in a solid-phase binding assay using immunoimmobilized IDE. Since IDE binds **insulin** with 600-fold greater affinity than it does **insulin-like growth factor I** (25 nM and .apprx.16,000 nM, resp.), the first set of analogs studied were hybrid mols. of **insulin** and **IGF I**. **IGF I** mutants [**insB1-17,17-70**]IGF I, [**Tyr55,Gln56**]IGF I, and [**Phe23,Phe24,Tyr25**]IGF I have been synthesized and share the property of having **insulin-like** amino acids at positions corresponding to primary sites of cleavage of **insulin** by IDE. Whereas the first 2 exhibit affinities for IDE similar to that of wild type **IGF I**, the [**Phe23,Phe24,Tyr25**]IGF I analog has a 32-fold greater affinity for the immobilized enzyme. Replacement of Phe-23 by Ser eliminates this increase. Removal of the 8 amino acid D-chain region of **IGF I** (which has been predicted to interfere with binding to the 23-25 region) results in a 25-fold increase in affinity for IDE, confirming the importance of residues 23-25 in the high-affinity recognition of IDE. A similar role for the corresponding (**B24-26**) residues of **insulin** is supported by the use of site-directed mutant and semisynthetic **insulin** analogs. **Insulin** mutants [**B25-Asp**] **insulin** and [**B25-His**] **insulin** display 16- and 20-fold decreases in IDE affinity vs. wild-type **insulin**. Similar decreases in affinity are obsd. with the C-terminal truncation mutants [**B1-24-His25-NH2**] **insulin** and [**B1-24-Leu25-NH2**] **insulin**, but not [**B1-24-Trp25-NH2**] **insulin** and [**B1-24-Tyr25-NH2**] **insulin**. The truncated analog with the lowest affinity for IDE ([**B1-24-His25-NH2**] **insulin**) has one of the highest affinities for the **insulin** receptor. Thus, a region of the **insulin** mol. responsible for its high-affinity interaction with IDE was identified. Although the same region has been implicated in the binding of **insulin** to its receptor, data suggest that the structural determinants required for binding to receptor and IDE differ.

RC 660 A1 7 4 (micro)

L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 91340787 EMBASE
DN 1991340787
TI Receptor binding and tyrosine kinase activation by **insulin**
analogues with extreme affinities studied in human hepatoma HepG2 cells.
AU Drejer K.; Kruse V.; Larsen U.D.; Hougaard P.; Bjorn S.; Gammeltoft S.
CS Novo-Nordisk A/S, DK-2880 Bagsvaerd, Denmark
SO Diabetes, (1991) 40/11 (1488-1495).
ISSN: 0012-1797 CODEN: DIAEAZ
CY United States
DT Journal; Article
FS 003 Endocrinology
037 Drug Literature Index
LA English
SL English

=> d 7 hit

L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Receptor binding and tyrosine kinase activation by **insulin**
analogues with extreme affinities studied in human hepatoma HepG2 cells.
AB The **insulin**-receptor affinity of five human **insulin**
analogues with one to four amino acid substitutions was measured with
human hepatoma cells (HepG2). The binding affinities ranged from 0.05% for
Asp(B25) insulin, 18% for **Asp**
(B9),**Glu(B27) insulin**, 80% for **Asp(B28) insulin**, and
327% for **Asp(B10) insulin** to 687% for
His(A8), His(B4), Glu(B10), His(B27) insulin relative to human
insulin. Binding constants obtained by competition experiments at
steady state with [¹²⁵I]Tyr(A14)-labeled **insulin** and unlabeled
analogues and by kinetic studies with [¹²⁵I]Tyr(A14)-labeled analogues and
insulin gave essentially the same values. The kinetic studies
showed that differences in affinity between analogues were due to
differences in both dissociation and association rate constants. The
affinity for **insulinlike growth factor I receptor** was low,
ranging from <0.005% for **Asp(B25) insulin** to
0.6% for **His(A8), His(B4), Glu(B10), His(B27) insulin**. The
potencies of **insulin** analogues in activation of the tyrosine
kinase of solubilized and partially purified **insulin** receptors
from HepG2 cells, measured with the exogenous substrate poly(Glu80-Tyr20),
ranked in the same order as the binding affinities, the actual values
being somewhat elevated for the high-affinity analogues, however. We
conclude that these human **insulin** analogues are active in
insulin-receptor binding and tyrosine kinase stimulation but show
wide variation in affinity.

CT Medical Descriptors:

*hepatoma cell

*kidney

article

controlled study

human

human cell

priority journal

Drug Descriptors:

*insulin receptor

*insulin: PD, pharmacology

*insulin: CM, drug comparison

*insulin derivative: PD, pharmacology

*insulin derivative: CM, drug comparison

*protein tyrosine kinase: EC, endogenous compound

RN (insulin) 9004-10-8; (protein tyrosine kinase) 80449-02-1

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:491611 BIOSIS
DN PREV199799790814
TI Metabolically inactive insulin analog prevents type I diabetes
in prediabetic NOD mice.
AU Karounos, D. G. (1); Bryson, J. S.; Cohen, D. A.
CS (1) Dep. Intern. Med., Univ. Kentucky Med. Cent., 800 Rose St., Rm. MN520,
Lexington, KY 40536-0084 USA
SO Journal of Clinical Investigation, (1997) Vol. 100, No. 6, pp. 1344-1348.
ISSN: 0021-9738.
DT Article
LA English

=> d 9 ab

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AB The purpose of this study was to determine the relative importance of the
metabolic effects of insulin for diabetes prevention by
administering insulin or an inactive insulin analog by
daily subcutaneous injections to prediabetic mice. A recombinant monomeric
human insulin analog, which does not bind to the insulin
receptor as a consequence of an alteration of a single amino acid at
position 25 of the B chain, was shown to be equally effective at diabetes
prevention as was intact insulin. In contrast to native
insulin, the insulin analog did not cause hypoglycemia
after subcutaneous injection. The insulin analog, however,
protected young adult mice from diabetes, even when it was initiated after
the onset of extensive lymphocytic infiltration of the islets. Thus,
preventative therapy by daily subcutaneous injections of insulin
does not require the hypoglycemic response, or binding to the
insulin receptor to prevent the onset of type I diabetes.

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WEST Search History

DATE: Friday, July 25, 2003

<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
side by side			result set
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR</i>			
L13	L12 and insulin\$	7	L13
L12	Worsaae	26	L12
L11	L10 and insulin\$	16	L11
L10	dyrberg	29	L10
L9	L8 and insulin\$	1	L9
L8	Mandic	46	L8
L7	L4 near10 (acid or acidic or hydrophilic)	17	L7
L6	L5 not l1	0	L6
L5	L4 near10 (Asp or aspart\$)	2	L5
L4	(insulin\$)near10(B25)	36	L4
L3	L2 not l1	0	L3
L2	(asp or asparty or aspartat\$)near3 (B25)or Asp-B25	2	L2
L1	(insulin\$) and (asp or asparty or aspartat\$)near3 (B25)	2	L1

END OF SEARCH HISTORY